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the network and new tests that might be offered is needed urgently. A recent report by an expert working group for the NHS Executive and the Human Genetics Commission has recommended that the Department of Health acts now to consolidate this network.[1]

The identification of genes involved in common diseases and responses to drug treatment raises further and even greater uncertainties for the future provision of services. Recent developments in cancer genetics provide useful insights. Several genes conferring a high risk of breast, ovarian, or colorectal cancer were identified during the 1990s. These genes seem to account for less than 5% of all cases but a higher proportion of cases with a strong family history and young age at diagnosis. Publicity surrounding these discoveries has generated unprecedented pressure on regional genetic centres, much of it from families in which the genes concerned are unlikely to be involved. Although centres are responding by establishing filtering mechanisms to identify the minority of families at high genetic risk, the concerns of those at moderate or low risk can only be effectively dealt with in partnership with primary care.

Further surges in demand for genetic information and testing in relation to common polygenic disorders are likely, although enthusiasts may be prone to overestimate this demand and the utility of genetic testing for complex polygenic diseases. By contrast, the recent genetics scenario project from the Nuffield Trust has emphasised the appreciable potential of pharmacogenomics to tailor drug choice and dosage in individual patients.[2]

In the face of these new developments there is a clear need for action. Firstly, a system throughout the United Kingdom must be consolidated for the evaluation and implementation of new genetic tests for rare genetic diseases. The planning of resources and manpower for counselling and clinical services, which are integral to genetic testing, must be included in this process. The recent formation of a Genetics Commissioning Advisory Group within the National Specialist Commissioning Advisory Group is an important development in this regard. Secondly, regional genetic centres must form partnerships with primary care and with public health to evaluate new developments in the genetics of common diseases. Thirdly, new partnerships will be required with other hospital based specialties. Pathology laboratories, for example, increasingly have the potential to identify somatic clues indicative of inherited mutant genes. For instance, detection of instability affecting repetitive DNA sequences in cancer tissue can suggest hereditary non-polyposis colorectal cancer. The increasing accessibility of DNA technology will force re-examination of the traditional divide between the analysis of somatic and germline mutations.

The experience of regional genetic centres in dealing with issues of confidentiality and the implications of genetic testing for family members will be invaluable in relation to these clinical and laboratory challenges. If resourced they are well placed to provide education and training on inherited disease for other specialties. And as Donnai and Elles suggest, the developing role of the genetic counsellor may be particularly relevant to primary care.

Competing interests: None declared.

1 Laboratory services for genetics—report of an expert working group to the NHS Executive and the Human Genetics Commission, Aug 2000. www.doh.gov.uk/genetics/laboratory.htm (accessed April 2001).
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The complexities of predictive genetic testing

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Predictive genetic testing is the use of a genetic test in an asymptomatic person to predict future risk of disease. These tests represent a new and growing class of medical tests, differing in fundamental ways from conventional medical diagnostic tests. The hope underlying such testing is that early identification of individuals at risk of a specific condition will lead to reduced morbidity and mortality through targeted screening, surveillance, and prevention. Yet the clinical utility of predictive genetic testing for different diseases varies considerably. We explore here the factors that contribute to this variation and which will dictate the utility of any of these new tests now or in the future.

Summary points

- Predictive genetic testing has considerable potential for accurate risk assessment and appropriate targeting of screening and preventive strategies
- Most predictive tests carry a degree of uncertainty about whether a condition will develop, when it will develop, and how severe it will be
- The value of a predictive test depends on the nature of the disease for which testing is being carried out, how effective treatment is, and the cost and efficacy of screening and surveillance measures
- Predictive testing must be tailored to individuals' preferences and the needs and experience of families

Methods and definition of terms

The observations in this paper derive from our experience in clinical medicine, medical genetics, genetic counselling, and molecular biology and from participation in educational programmes for generalists on medical genetics. The definition of utility used here

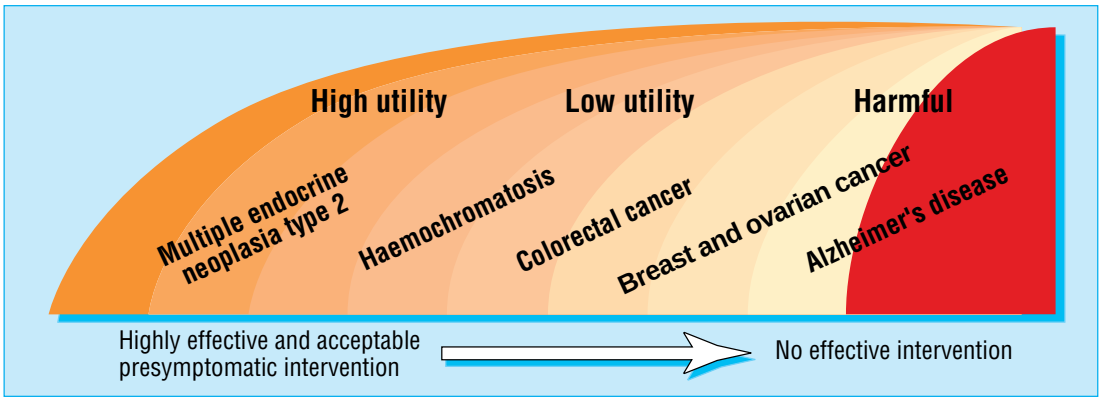

Fig 1 Utility in predictive genetic testing

encompasses all aspects of a test (individual and societal) that render it more or less useful in the clinical arena.

Difference from conventional medical testing

Current and future use

A conventional medical diagnostic test, such as a blood count or an imaging study, defines something about the patient's current condition. Although such information may have implications for the future, its overwhelming utility lies in the information it provides about the patient's current state.

A predictive genetic test, in contrast, informs us only about a future condition that may (or may not) develop. The identified risk is sometimes high—for example, in a positive test for Huntington's disease)—but always contains a substantial component of uncertainty, not only about whether a specific condition will develop, but also about when it may appear and how severe it will be. Predictive genetic tests often carry a further element of uncertainty: the interventions available for individuals at risk are often untested, and recommendations may be based on presumed benefit rather than observations of outcomes.[1 2]

These uncertainties contrast with the presentation of predictive genetic testing in the popular media, which often fosters an illusion that genetic risk is highly predictable and determinative.[3] A *New York Times* article, for example, recently described a "genetic report card" that would predict a baby's health history at birth.[4] In fact, uncertainties inherent in most genetic tests represent a major limitation to their clinical utility.

Individual versus family

Whereas conventional diagnostic testing rarely has medical importance for anyone other than the person tested (except in the case of communicable diseases) predictive genetic testing typically has direct implications for family members. Concern for relatives may be an important motivating factor for a patient wanting to undergo such testing; some family members, however, may resist participating in the testing because they prefer not to have information about their genetic risk. The utility of a predictive genetic test will therefore depend on whose point of view is considered.

Utility of predictive genetic testing for different diseases

An examination of predictive genetic testing in various diseases helps to identify factors that determine utility. Figure 1 shows the degree of utility for various diseases (ranked according to how clinically useful testing currently is). These diseases are discussed below, from those for which testing is most useful through to those for which testing is least useful or even harmful.

Multiple endocrine neoplasia type 2

The rare disorder multiple endocrine neoplasia type 2 results from mutations in the RET proto-oncogene. People with the disorder are almost certain to develop medullary thyroid carcinoma unless they undergo prophylactic thyroidectomy.[5] Studies comparing children with multiple endocrine neoplasia type 2 who underwent thyroidectomy with those who did not, offer compelling evidence that such surgery reduces the likelihood of dying from cancer.[6] Predictive genetic testing makes it possible to identify those who will benefit from surgery.

This example illustrates that when predictive genetic testing strongly predicts a deleterious clinical outcome and an efficacious early intervention exists, it is of high utility. Indeed, such testing for multiple endocrine neoplasia type 2 is the accepted standard of care for individuals at risk.[7]

Haemochromatosis

Haemochromatosis is an uncommon (but not rare) condition of tissue iron deposition, leading to diabetes, cirrhosis, heart disease, arthritis, and gonadal dysfunction.[8] Phlebotomy is a simple and effective preventive treatment, and predictive genetic testing is therefore useful to raise suspicion of this often elusive diagnosis. Testing is less useful for haemochromatosis than for multiple endocrine neoplasia type 2, however, because of low predictive value.[9 10]

Although excess iron accumulation results from a genetic predisposition, other factors contribute to the development of clinically important iron overload, including sex, diet, and exposure to liver toxins such as alcohol. Thus the penetrance of the haemochromatosis genotype (the proportion of individuals with genetic susceptibility who will develop the associated clinical condition) is low. The resultant uncertainty limits the utility of predictive genetic testing because pre-

Factors affecting utility of predictive genetic testing

Increased utility	Decreased utility
High morbidity and mortality of disease	Low morbidity and mortality of disease
Effective but imperfect treatment	Highly effective and acceptable treatment
High predictive power of the genetic test (high penetrance)	Poor predictive power of the genetic test (low penetrance)
High cost or onerous nature of screening and surveillance methods	Availability of inexpensive, acceptable, and effective screening and surveillance methods
Preventive measures that are expensive or associated with adverse effects	Preventive measures that are inexpensive, efficacious, and highly acceptable—for example, vaccination

ventive action based only on the results of such testing would subject many individuals who would never develop clinical sequelae to unnecessary phlebotomy.

Colorectal cancer

About 5-10% of colorectal cancer results from inheritance of a few highly penetrant gene mutations that confer a high lifetime risk of the disease.[11] Predictive genetic testing can be useful when family history suggests increased risk—for example, three or more affected relatives, with one in whom the disease was diagnosed before age 50[12]—and is compatible with a diagnosis of hereditary non-polyposis colon cancer. Affected individuals have about a 70% lifetime risk of colorectal cancer.[12] Periodic colonoscopic surveillance of these individuals reduces the development of colorectal cancer by 62% when compared with unscreened controls,[13] showing the utility of predictive genetic testing in this circumstance.

However, hereditary non-polyposis colon cancer involves other cancer risks as well. Affected women have a high risk of endometrial cancer, as well as increased risks of ovarian cancer, other gastrointestinal cancers, and cancers of the ureteral tract.[12] No established surveillance strategies are available for these other cancers.[2] Thus predictive genetic testing provides an established outcome benefit for only one of the risks identified, and therefore although useful, it provides less clear cut benefit than in a condition such as multiple endocrine neoplasia type 2.

Breast and ovarian cancer

About 5-10% of breast and ovarian cancers result from the inheritance of mutations in the BRCA1 or BRCA2 gene.[14] Predictive genetic testing for breast and ovarian cancer, as for hereditary non-polyposis colon cancer, can be useful to identify those at increased risk. In both breast and ovarian cancer, however, utility is limited because of considerable uncertainty about the predictive value of the test.

A woman carrying a mutation in the BRCA1 or BRCA2 gene may develop breast cancer, ovarian cancer, both cancers, or neither. Penetrance estimates range from 36-85% for breast cancer and 10-44% for ovarian cancer.[15–17] Moreover, the age at which cancer occurs is widely variable. These uncertainties probably reflect a combination of factors, including the environment, modifying genes, the nature of a woman's specific mutation, and purely stochastic processes.

> "Never make predictions . . . especially about the future"
>
> Samuel Goldwyn Sr, Hollywood producer

The utility of predictive genetic testing for breast and ovarian cancer is further limited by the nature of available surveillance and prevention strategies. Starting mammography at age 25 to 35 is recommended for carriers of the BRCA1 or BRCA2 gene, but the efficacy of this early surveillance is unknown.[1] Because mammography is already widely encouraged for women aged over 40 (in the United States) or 50 (in the United Kingdom), information on genetic susceptibility is less relevant at later ages. Finally, adequate surveillance for ovarian cancer is not available.[1]

Chemoprevention with tamoxifen shows promise for reducing risk of breast cancer,[18] but conflicting data exist.[19 20] Moreover, chemoprevention increases risk of endometrial cancer and venous thromboembolic disease. Oral contraceptives may reduce risk of ovarian cancer but may also increase risk of breast cancer.[21] Prophylactic oophorectomy and mastectomy are reasonable options for some women and seem to be effective in reducing cancer risk.[22 23] Such measures carry substantial burdens, however, and mastectomy in particular is not widely accepted by women at risk.[24]

In short, knowledge of an inherited predisposition to breast or ovarian cancer does not lead to simple, straightforward measures to reduce risk, thus limiting the utility of predictive genetic testing.

Alzheimer's disease

Alzheimer's disease illustrates the potential for predictive genetic testing to cause harm. Measurement of the apolipoprotein E genotype can predict risk of developing Alzheimer's disease in people of European descent.[25 26] Two copies of the apolipoprotein E4 gene (present in 2% of the general population[25 26]) are associated with a 10-fold increased risk of Alzheimer's disease[25]; one copy is associated with a twofold increased risk, and the inheritance of an apolipoprotein e2 allele is protective.[26] Thus a positive test is an imprecise measure of risk and could result in anxiety, stigmatisation, or discrimination. The principle of avoiding harm suggests that currently such testing would generally be unethical because no effective prevention is available.[27 28]

Factors affecting utility

The ideal context, therefore, is a highly predictive test for a disease that is serious and incurable but preventable by means that are imperfect or expensive. The table shows factors affecting utility of predictive genetic testing.

Severity of disease and availability of effective treatment

The utility of predictive genetic testing declines when a disease is curable. Testing for tuberculosis, for example, makes little sense, even though genetics contributes to susceptibility to the disease.[29] Similarly, as scientific advances make breast or colon cancer curable by increasingly innocuous means, the utility of predictive genetic testing will decline.

Screening and prevention

Effective and inexpensive screening methods also make predictive genetic testing less useful because these measures can be readily applied to the entire population. Testing for hypertension makes little sense—despite evidence of strong genetic contributors

to this condition[30]—because universal screening and treatment are the rule. As the expense of screening rises, predictive genetic testing becomes more appealing. Thus, if magnetic resonance imaging (which is expensive) were shown to be superior to mammography (less expensive) in screening for breast cancer, testing could target those who would benefit most.

Available preventive measures must be either imperfect or expensive for predictive genetic testing to be of high utility. Testing makes sense in women at high risk of breast or ovarian cancer if they are considering oophorectomy or mastectomy: a positive test would confirm risk and support the use of invasive, imperfect interventions. When prevention is simple, however, the value of testing decreases. Vaccination is so cheap, safe, and effective that universal administration is rational. Thus testing has no utility in measles, mumps, or rubella despite evidence of genetic differences in susceptibility to infectious disease.[29] The same would be true if an effective, safe, and inexpensive vaccination existed for breast cancer.

Perceptions of utility

Family history and experience are important factors in determining how an individual perceives the utility of predictive genetic testing. Figures 2 and 3 show how a woman's perception of the utility of testing for risk of breast cancer, for example, can vary depending on whether other close relatives have died of the disease or on her own family structure.

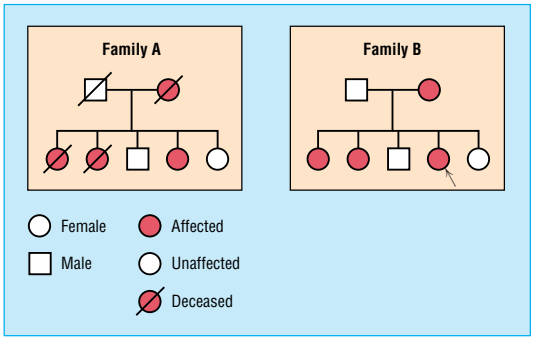

Fig 2 Families' experiences affect their perceptions of utility of predictive genetic testing. The affected woman in family A, whose sisters and mother died of breast cancer, may perceive chemoprevention or prophylactic surgery favourably, and welcome the guidance that predictive genetic testing can provide in making such decisions. Her counterpart (arrowed) in family B may perceive breast cancer to be a less traumatic disease and feel comfortable with routine surveillance, thus lessening the utility of testing for her

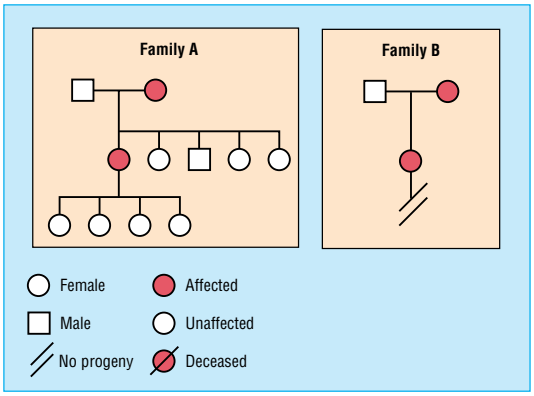

Fig 3 Family structure affects perceptions of utility of predictive genetic testing. The woman with four daughters unaffected by breast cancer (family A) may feel that information on risk may be of benefit for their sake, whereas for the woman with no progeny (family B) the utility of such testing declines

Educational resources

National Society of Genetic Counselors. Predisposition genetic testing for late-onset disorders in adults. *JAMA* 1997;278:1217. (Position paper of the NSGC.)

American Society of Clinical Oncology. Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility. *J Clin Oncol* 1996;14:1730.

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www.nsgc.org/GeneticCounselingYou.asp

www.geneticheath.com

www.geneclinics.org/

www.cancergenetics.org/home.htm

www.myriad.com

http://cancernet.nci.nih.gov/genetics/breast.htm

Conclusion

Predictive genetic testing has great potential for accurate risk assessment and for guiding the use of an expanding armamentarium of screening and prevention methods. The utility of testing varies widely, however, depending on the magnitude of risk, the accuracy of risk prediction, options available to reduce risk, an individual's previous experience, and the needs and experience of family members. In addition, the utility of a given predictive genetic test is likely to change over time as knowledge grows, new strategies for prevention are developed, and costs change. The complexity of these factors calls for discussions about testing that are highly tailored to the testing context and the individual's needs and preferences.

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Genetic risk and behavioural change

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Predictive genetic testing is currently used mainly for untreatable conditions, such as Huntington's disease, or prenatal detection of serious genetic disorders such as cystic fibrosis. Prenatal tests are usually accompanied by an offer of termination of affected pregnancies. Genes have now been isolated that are associated with potentially preventable diseases such as heart disease and cancer and with increased risk from smoking and obesity. This has raised the possibility of providing predictive information to many more people. Such information may eventually reduce disease by facilitating the development of better targeted and more effective treatment.

Informing people of their genetic susceptibility to disease may motivate them to change their behaviour to reduce their risks. However, changing behaviour is often difficult. In this article we review the limited evidence concerning behavioural responses to genetic information on risk. We use this and the literature on behavioural change to consider if and how behaviour might be changed in response to genetic information.

Summary points

- Changing behaviour is difficult
- Behavioural change is most likely in motivated people who participate in effective interventions
- Providing people with genetic information on risk may not increase their motivation to change behaviour and in some cases may decrease motivation
- Behavioural change may be more likely if people are persuaded that changing their behaviour can reduce the risk of an adverse health outcome and they are given access to evidence based interventions
- Further research is needed to evaluate programmes in which genetic risk information is given, including evaluation of different ways of giving information
- Effective interventions to change behaviour after provision of information on risk need to be developed

Methods

We searched Medline, PsycINFO, and the Social Science Citation Index using the following terms: health behavior; illness behavior; genetic screening or mass screening; cancer screening, health screening, mammography, or preventive medicine; genetic counselling, genetic disorders, genetic linkage, or genetics; and at risk populations. In addition, we searched citations of key papers, recent reviews of the subject, and conference proceedings (using the Web of Science).

Changing health related behaviour

Just telling people that they are at risk of developing a disease is rarely sufficient to change behaviour.[1] The interventions that are most likely to work are those that